PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	26.04.2005
Applicant's or agent's file reference: RLL-231WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 02/05213	10.12.2002	10.12.2002

Applicant
RANBAXY LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel. +49 89 2399-8012

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-231WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 02/05213	International filing date *(day/month/year)* 10.12.2002	Priority date *(day/month/year)* 10.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D239/42		
Applicant RANBAXY LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.07.2004	26.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fink, D Telephone No. +49 89 2399-8701

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/05213

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-9 as originally filed

Claims, Numbers

1-33 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: EP-A-0521471;

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-33** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The process of the present independent **claim 1** for the preparation of *rosuvastatin* is novel over the process of the prior art **D1** (cf., page 2, line 53 - page 4, line 5; and the examples 1 and 7) because of the **novel** 6-***cyano***-hex-1-en intermediates of the present formulae ***IV***, ***V*** and ***VI*** (cf., the corresponding ***methyl hept***-6-en***oates*** **6**, **7** and (**Ib-1**) according to the example 1 of **D1**).

The compounds of the present independent **claims 30-33** (cf., the *precursor / intermediate* compounds of the present formulae **II**, **IV**, **V** and **VI**) are **not** known from the prior art (**D1**).

The present independent process **claims 19** (preparation of **VI**), **20** (preparation of **V**) and **22** (preparation of **IV**) are therefore also novel (over **D1**).

The present independent process **claim 25** (which is also directed to the preparation of *rosuvastatin*) comprises the **novel** condensation step according to the present **claim 22**) and is thus also novel (over **D1**).

2. INVENTIVE STEP (Article 33(3) PCT):

The present application also satisfies the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-33** involves an inventive step (Rule 65(1)(2) PCT):

2.1. Document **D1** - which represents the **closest prior art** - also teaches a process for the preparation of *rosuvastatin* (cf., page 2, line 53 - page 4, line 5; and the examples 1 and 7).

2.2. The process of the present independent **claim 1 differs** from the aforesaid **D1** process because of the **novel** 6-***cyano***-hex-1-en intermediates of the present formulae ***IV***, ***V*** and ***VI*** (cf., the present reaction sequence:

5-(^{t}butyl-dimethyl-silanoxy)-***6-cyano***-3-oxo-hex-1-ene derivative **IV** →
5-*hydroxy*-***6-cyano***-3-oxo-hex-1-ene derivative **V** →
3,5-di*hydroxy*-***6-cyano***-hex-1-ene derivative **VI** →
rosuvastatin

and the reaction sequence according to **D1** (cf., examples 1, 7):

methyl 3-(^{t}butyl-dimethyl-silanoxy)-5-oxo-***hept***-6-en***oate*** derivative **6** →
methyl 3-*hydroxy*-5-oxo-***hept***-6-en***oate*** derivative ***7*** →
methyl *3*,5-di*hydroxy*-***hept***-6-en***oate*** derivative (**Ib-1**) → →
rosuvastatin).

2.3. In the light of **D1** the **problem** underlying the present application resides in the provision of a <u>further</u> process for the preparation of *rosuvastatin*.

2.4. Accordingly, the present application proposes the process of the present **claim 1** in order to **solve** the given problem.

2.5. It would appear that this solution involves an inventive step (Article 33(3) PCT), because the available prior art (**D1**) does **not** teach or suggest a process using 6-***cyano***-hex-1-en intermediates.

2.6. It is therefore considered that the subject-matter of the present **claim 1** involves an inventive step as set forth in Article 33(3) PCT.

2.7. As the process of the present **claim 1** is non-obvious with respect to **D1**, it is considered that the ***cyano***- substituted *precursors* / (key) *intermediates* of the present **claims 30-33**, the processes for their preparation according to the present **claims 19, 20** and **22**, and the process of the present **claim 25**, likewise involve an inventive step as set forth in Article 33(3) PCT.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-33** concerns chemical processes and chemical compounds and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

4.1. The present **claim 25** is unclear in the sense of Article 6 PCT, because
(i) step (b) concerns a *deprotection* step rather than an *esterification* step (cf., page 22, line 1 "...*esterifying* ..... to give an *ester*..." and line 5 "...reducing the *ester*..."), and
(ii) the *reduction* of step (c) should presumably yield the 3-hydroxy derivative (rather than the 3-oxo derivative of formula X).

It is furthermore noted that the formulae IX and X of the present **claim 25** correspond to the present formula V (cf., the requirements of Rule 10.2 PCT: consistent terminology).

4.2. The name "....***cyano*** (2S)-2-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-triphenyl-phophanylidene hexane***nitrile***..." (cf., the compounds of formula **II**) in the present claims 1, 19, 20, 22 and 25 is obviously incorrect (cf., the **two** cyano functionalities) (Article 6 PCT; clarity).

4.3. The "H_3C-$S(O)_2$-N-***C***" group in the formula **IV** of the present claims 1, 19, 20, 22, 25 and 31, and the "H_3C-$S(O)_2$-N-***X***H_3" group in the formula **III** of the present claims 20, 22 and 25 should obviously read "H_3C-$S(O)_2$-N-***CH_3***" (Article 6 PCT; clarity).